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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,570	02/19/2004	Nadine Carozzi	045600/274144	5780

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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	**PAPER NUMBER**
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/782,570	CAROZZI ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *04 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,19,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,19,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4 May 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-11, 19 and 22-23 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The objection to claims 1 and 19 because of informalities is withdrawn in light of Applicant's amendment of the claims

Claim Rejections - 35 USC § 112

4. Claims 1-11, 19 and 22-23 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding SEQ ID NO:2 or 4, host cells, plants, plant cells and seeds comprising them, and method of using them to make SEQ ID NO:2 or 4, does not reasonably provide enablement for nucleic acids encoding pesticidal protein with 90% identity to SEQ ID NO:2 or 4, nucleic acids with 90% identity to SEQ ID NO:1 or 3, or a complement of those nucleic acids, host cells, plants, plant cells and seeds comprising them, and method of using them to make a pesticidal protein with 90% identity to SEQ ID NO:2 or 4 and a pesticidal protein encoded by a nucleic acid with 90% identity to SEQ ID NO:1 or 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the Office action mailed 6 February 2007. Applicant's arguments filed 4 May 2007 have been fully considered but they are not persuasive.

Applicant urges they do not have to provide support for making a protein with 223 amino acid substitutions with no experimentation, only with no undue experimentation (response pg 7).

This is not found persuasive because it would require undue experimentation to make a protein with 223 amino acid substitutions, given the insufficient guidance in the specification and the unpredictability of making amino acid substitutions in Cry proteins.

Applicant urges *Wands* does not require a working example of every pesticidal protein that could be used to practice the present invention (response pg 7).

This is not found persuasive. A working example of every pesticidal protein that could be used to practice the present invention is not being required; a teaching of how to make the full scope of claimed nucleic acids that encode pesticidal proteins is required, however.

Applicant urges the examiner bases the conclusion of lack of enablement solely on the number of possible nucleic acids having the recited percent identity to SEQ ID NO:1 or 3 and ignores the other *Wands* factors (response pg 7).

This is not found persuasive. The rejection presented in the Office action mailed 6 February 2007 did not base any conclusion on the number of possible nucleic acids having the recited percent identity to SEQ ID NO:1 or 3 nor did it ignore the other *Wands* factors. The breadth of the claim was compared to the amount of direction provided by the inventor, and that guidance was found lacking. The state of the prior art, the nature of the invention, and the existence of working examples, the quantity of experimentation needed to make or use the invention based on the content of the disclosure, the level of one of ordinary skill and the level of predictability in the art were also discussed.

Applicant urges that sufficient guidance for making and using the recited sequences is present on pg 8-13, the sequences are limited by percent identity and function, Cry proteins are well-known, citing Crickmore, and the necessary techniques are routine (response pg 7-8).

This is not found persuasive. Limiting the percent identity of the claimed nucleic acid and requiring a function do not teach which amino acid substitutions may be made in the proteins. The guidance on pg 8-11 merely discusses fragment size, percent identity, and calculation of percent identity. However, guidance for determining percent identity does not teach the necessary and sufficient structural features of the claimed nucleic acids, and does not teach which amino acids could be substitutive with which other amino acids. The guidance on pg 12-13 is discussed above; it fails to sufficiently teach which amino acid substitutions to make in SEQ ID NO:2 or 4, given the unpredictability in making amino acid substitutions in cry proteins.

According to the naming system defined by Crickmore, SEQ ID NO:2's less than 28% identity to other Cry proteins places it in a different primary rank and places it in outlying Cry lineages (pg 808, left column, paragraph 2-4; Fig. 1), emphasizing the differences between SEQ ID NO:2 and other known Cry proteins. Making 223 amino acid substitutions in SEQ ID NO:2 and successfully making a functional cry protein is not taught by Crickmore or the cited portions of the specification.

Applicant urges that one would only need to make the claimed variants and assay them for activity using routine methods; thus the amount of experimentation is not undue, which

Hybridtech defines as no disclosure of starting material or conditions under which a process may be carried out (response pg 8-9).

This is not found persuasive. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) at pg 1404 states:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* (230 USPQ at 547). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

"Undue experimentation" is not limited to situations in which there is no disclosure of starting material or conditions under which a process may be carried out. *Hybridtech*'s definition is not the only one.

Making the claimed variants and assay them for activity would require undue experimentation because the specification does not provide sufficient guidance as to which 223 amino acid substitutions can be made in SEQ ID NO:2. Thus, one would need to randomly make nucleic acids encoding proteins with 223 amino acid substitutions and test them. Because this would require trail and error experimentation and because of the likelihood of protein inactivation (see Guo et al, pg 9209, right column, paragraph 2) and the unpredictability of amino acid interactions in cry proteins (Aaronson et al, paragraph spanning the columns on pg 7; de Maagd et al, 1999, pg 4369, column 1, paragraph 1; de Maagd et al, 2001, pg 194, right column, paragraph 3), this experimentation would be undue.

Applicant urges that that Genentech states that the specification must supply the novel aspects of the invention, and in Genentech no starting materials were disclosed, while here there

is a working example and guidance; the absence of these are is undue experimentation (response pg 9).

This is not found persuasive. The instant rejection is a scope of enablement rejection; the invention is enabled for nucleic acid encoding SEQ ID NO:2 or 4. The specification, however, does not provide adequate guidance for making 223 amino acid substitutions in SEQ ID NO:2 or making 208 substitutions in SEQ ID NO:4. The art indicates that even though much is known about Cry protein structure, not enough is known about the structure/function relationship to predict a protein's toxicity.

Applicant urges the specification provides a starting material and description regarding amino acid substitutions, in the form of conserved residues and domains and Fig 1 (response pg 9-10).

This is not found persuasive. Fig. 1 has only 5 positions that are identical among all the proteins in the Figure, and 7 positions that have only conservative substitutions among all 239 amino acids as given in the specification, and 141 amino acids as those regions are defined in the art. Together, these amino acids total less than 25% of the SEQ ID NO:2's length. The art indicates that more guidance is needed.

The findings and teachings of Aaronson et al, Angsuthanasombat, de Maagd et al, Tounsi et al and de Maagd et al, 2001, as well as the references cited by Applicant (Jenkins, Rajamohan, Lee, Schartz and Masson) show that interactions between amino acids in Cry proteins is much more complex than can be predicted from guidance suggesting only making conservative

substitutions. De Maagd et al (2001) specifically teaches that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2).

Applicant urges that *Amgen* supports the enablement of the instant invention because here there is no claim for all analogs; because the claims are limited by percent identity the are drawn to similar analogs, which the Court justified in *Amgen* (response pg 10).

This is not found persuasive. The toxicity of the variants proteins encoded by the claimed nucleic acids is not known, nor can it be predicted.

Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991) at pg 1028

> Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, **with attendant uncertainty as to what utility will be possessed by these analogs**, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. *(emphasis added)*

Applicant urges the specification indicates that substitutions would not be made in conserved amino acids or motifs, citing pg 13, lines 10-11 (response pg 10-11).

This is not found persuasive. Pg 13, lines 10-11 actually states "However, one of skill in the art would understand that functional variants may have minor conserved or nonconserved alterations in the conserved residues." Further, as discussed above, the conserved amino acids or motifs cover less than 25% of the SEQ ID NO:2's length. The art indicates that more is needed to teach how to successfully make the claimed nucleic acids.

Applicant urges Guo's results only suggest that a large number of substitutions were not produced, not that they could not be; the instant specification provides guidance for which amino acids are not likely to tolerate random substitution (response pg 11).

This is not found persuasive. Gou's random mutagenesis method allowed substitutions wherever they could occur. Given that the probability that a single random amino acid substitution inactivates an enzyme is 34%, making 223 amino acid substitutions in SEQ ID NO:2 is unlikely to be successful.

Applicant urges detailed information about Cry secondary and tertiary protein structure was known, citing Li and Morse; they provide guidance for determining regions that would tolerate modification (response pg 11-12).

This is not found persuasive because general knowledge of Cry secondary and tertiary protein structure does not provide information on which amino acids are critical for toxicity toward *L. lineolaris*, which is the function taught in the specification. Proteins with up to 223 amino acid substitutions relative to SEQ ID NO:2 would likely have a very different insect toxicity than AXMI-007, if such toxins could even be made.

Applicant urges that one could choose possible modifications based on the regions conserved among protein family members, then test for pesticidal activity (response pg 12).

This is not found persuasive because there are no family members for AXMI-007 (SEQ ID NO:2). The instant Table 1 shows that AXMI-007 has 27% identity to cry4Aa, 25% identity to cry10Aa, and 25% identity to cry19Ba. According to the naming system defined by Crickmore, SEQ ID NO:2's less than 28% identity to other Cry proteins places it in a different primary rank to all these Cry lineages (pg 808, left column, paragraph 2-4; Fig. 1), emphasizing the differences between SEQ ID NO:2 and other known Cry proteins. Further, comparison to cry4Aa, cry10Aa or cry19Ba would not let one know which amino acids are critical for toxicity

toward *L. lineolaris*, the function of AXMI-007, as cry4Aa, cry10Aa and cry19Ba are all mosquito toxins.

Applicant urges that de Maagd et al 1999, Tounsi et al, Aaronson et al, and de Maagd et al 2001 support their argument that making substitutions in cry proteins is routine (response pg 12).

This is not found persuasive because none of these authors made up to 223 amino acid substitutions in a Cry protein, as encompassed by the claimed nucleotides. If Applicant were claiming nucleic acids encoding Cry proteins with a few amino acid substitutions relative to SEQ ID NO:2, the claims would be enabled. But given the unpredictability in making amino acid substitutions in Cry proteins and given the large number of substitutions encompassed by the claims, the claims are not enabled.

5. Claims 1-11, 19 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 6 February 2007. Applicant's arguments filed 4 May 2007 have been fully considered but they are not persuasive.

Applicant urges the claims recite percent identity, for which the methods for determining are routine, discloses a variant (SEQ ID NO:3); many Cry proteins are known in the art, as are

their structures and functions associated with particular structures, regions and motif, citing pg 2, 12 and the Fig 1 legend (response pg 14).

This is not found persuasive because the structures associated with particular the disclosed function, *L. lineolaris* toxicity, are not known in the art or described in the specification. The "variant" SEQ ID NO:3, which encodes the 694 amino acid long SEQ ID NO:4, is merely a 2085 nucleotide long fragment of the 2235 nucleotide long SEQ ID NO:1, which encodes the 744 amino acid long SEQ ID NO:2.

Applicant urges that it was known that cry proteins have three domains, a helix bundle, a three-sheet domain and a beta sandwich motif, citing Li, providing very specific and define structural parameters to the claimed sequences (response pg 14-15).

This is not found persuasive. These general characteristics are true of every Cry protein, including those with toxicity to lepidopterans, coleopterans, nematodes and mosquitoes, those that only work when associated with other Cry proteins, and those native proteins that do not appear to have any toxicity at all. These basic structures are merely characteristics of Cry proteins. They are not specifically associated with the disclosed function, *L. lineolaris* toxicity. de Maagd et al (2001) teaches that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2). Additionally, it is noted that the claims are not limited to nucleic acids encoding Cry proteins.

Applicant urges relevant motifs were known, including the domains taught by Li, and conserved regions taught in the specification (response pg 15).

This is not found persuasive because Li et al does not describe the structural features responsible for the claimed function. de Maagd et al, 1999, teach that that the crystal structure of Cry1C only allows for limited prediction of the exact structure of Cry1Aa (pg 4373, right column, paragraph 4); thus, Li's teaching is insufficient for describing the structure/function relationship of the claimed nucleic acids.

Applicant urges individual support for each species is not required; they have provided exemplary nucleotide and amino acid sequences and variants and fragments thereof, and numerous Cry proteins were known in the art, allowing one to envision that claimed invention (response pg 15-16).

This is not found persuasive because ones of skill in the art say that the relationship between structure and function is not well-known in Cry proteins. Aaronson et al, de Maagd et al, 1999, and de Maagd et al, 2001, make it clear that the correlation between that function and a structure is not sufficiently known in cry proteins as a whole, and the specification does not describe the motifs and amino acids required for SEQ ID NO:2 biological activity.

Applicant urges the recitation of a predictable structure is sufficient to satisfy the written description requirement (response pg 16).

This is not found persuasive because the correlation between structure and function is also required, but not provided by the instant specification. The relationship between structure and specific pesticidal function was not described in the specification.

Applicant urges the claim recite functional characteristics that distinguish the claimed sequences, as well as fragments (response pg 16).

This is not found persuasive. The specification does not describe the structure required for the function, nor does it describe the structural features that distinguish pesticidal protein-encoding nucleic acids with 90% identity to SEQ ID NO:1 or 3 from other nucleic acids with 950% identity to SEQ ID NO:1 or 3 or pesticidal proteins with 90% identity to SEQ ID NO:2 or 4 from other proteins with 90% identity to SEQ ID NO:2 or 4.

Conclusion

6. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

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enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Anne Kubelik, Ph.D.
July 18, 2007